I. Status of the Claims

Following entry of this amendment, claims 11 – 36, 40 – 45, 47 – 49, and 51 – 123 are pending. Claims 14, 25, 43, 71, 73, 75, 77, 79, 81, 83, 97, 104, and 111 are amended and claims 118 and 119 are added.

Claims 14, 25, 71, 73, 75, 77, 79, 81, 83, 97, 104, and 111 are amended to delete the second recitation of the term "analgesic" in each claim. In addition, the claims are amended to delete the recitation of "bronchodilators"; "corticosteroids"; and "anti-fungals." These categories of drugs are recited in new claims 118 and 119.

Finally, claim 43 is amended to clearly state that step (c) comprises formulating dry powder aggregates into an aerosol composition. Applicants note that the amendment of May 7, 2001, was intended to amend claim 43 in an identical manner as was indicated by the clean version of claim 43 in that amendment, but the amendment inadvertently failed to indicate that any change had been made in the marked-up version of claim 43. Applicants apologize for this oversight.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 13, 14, 25, 43, 45, 67, 68, 71, 73, 75, 77, 79, 81, 83, 97, 104-100, and 111 were rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. Applicants respectfully traverse this ground for rejection.

A. Rejection for Reciting a Markush Group Having Simultaneous Broad and Narrow Limitations

Claims 14, 25, 71, 73, 75, 77, 79, 81, 83, 97, 104, and 111 were rejected for allegedly reciting in each claim broad limitations together with narrow limitations falling within the broad limitations. Office Action at pages 2 to 3. The broad limitations are asthma therapies, analgesics, and fungal infection therapies, while the respective narrow limitations are

bronchodilators, corticosteroids, and anti-fungals. While Applicants respectfully disagree with this ground for rejection, the claims have been amended to delete the narrow limitations, which are now recited in dependent claims 118 and 119. This ground for rejection is now moot.

B. Rejection for Reciting the Term "Analgesics" Twice

Claims 14, 25, 71, 73, 75, 77, 79, 81, 83, 97, 104, and 111 were rejected as being allegedly indefinite because the claims "recite analgesics twice." Applicants respectfully traverse this rejection. Each of the claims recite "analgesics" once and "analgesic" once. For the sole purpose of expediting the prosecution of this case, the term "analgesic" has been deleted from the claims. This ground for rejection is now moot.

C. Alleged Lack of Antecedent Basis for the Term "Freeze-Dried Powder"

Claims 43, 67, 68, and 104 – 100 were rejected as being allegedly indefinite because the limitation "the freeze-dried powder" in claim 43 lacks sufficient antecedent basis. Applicants courteously traverse this rejection. As noted above, the amendment dated May 7, 2001, was intended to remove said limitation, but did not indicate so in the marked-up version of claim 43. Claim 43 has been amended to recite "the dry powder", rather than "the freeze-dried powder", for which sufficient antecedent basis exists. Applicants respectfully request that this rejection be withdrawn.

D. Alleged Indefiniteness for Reciting "Essentially Every Diluent"

Claims 13 and 45 were rejected as being allegedly indefinite because the term "essentially every diluent" in claims 13 and 45 "is a relative term" which is not defined by the claims. The Examiner further alleged that the specification does not provide a "standard for ascertaining the requisite degree", and concluded that "one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." Office Action at page 3. Applicants respectfully traverse this rejection.

Applicants' claims 13 and 45 recite that "essentially every diluent particle comprises at least one embedded nanoparticulate drug particle." The claim limitation "essentially every

diluent particle" indicates that most diluent particles, within experimental limits of detection, contain at least one embedded drug nanoparticle. This phrase is definite when viewed in the context of Applicants' disclosure. Specifically, the graphics on page 17, lines 10 – 18, demonstrate that a diluent particle contains embedded [drug] nanoparticles. *See also* page 18, lines 6 – 15, which describes the nature of aerosol compositions containing such diluent particles. Since the limitation "essentially every diluent particle" is clearly set forth in the specification, a person of ordinary skill in the art would be reasonably apprised of the scope of the claimed invention. Accordingly, Applicants' claims are definite and this ground for rejection should be withdrawn.

III. Claim Rejection Under 35 U.S.C. § 102

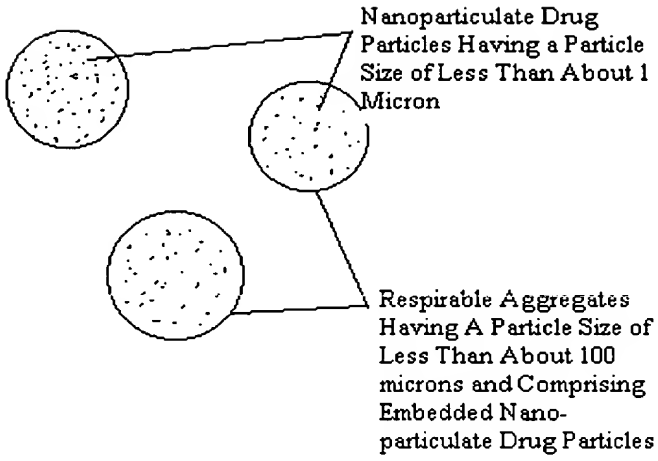
Claims 11 – 34, 40, 41, 44, 5, 47, 48, 51 – 62, 69 – 96, and 111 – 117 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Edwards et al., U.S. Pat. No. 5,985,309 ("Edwards"). Office Action at page 4. Applicants respectfully traverse this ground for rejection.

A. The Examiner's Basis for the Rejection

The Examiner asserted that Edwards discloses aerosol particle compositions that are less than 100 microns ("μm") in diameter and which have surfactants adsorbed thereon. Also, the Examiner stated that Edwards discloses the spray-drying and freeze-drying of the composition, and that Example 14 of Edwards teaches the "instant ranges" of Applicants' disclosed useful drug concentration.

B. Edwards Does Not Teach Applicants' Claimed *Drug* Particle Size; Rather, Edwards Only Teaches the Claimed *Aggregate* Particle Size

Applicants' claims recite two distinct particle sizes: (1) the particle size of the active agent or drug, which is less than about 1000 nm (*i.e.*, less than about 1 μm); and (2) the particle size of the aggregates of nanoparticulate drug particles, which is less than or equal to about 100 μm. The relationship between the aggregates and nanoparticulate drug particles can be graphically represented as follows:



Edwards teaches particulate compositions having a mean geometric diameter of between 5 μm and 30 μm. *See e.g.*, col. 5, lines 10 – 13 of Edwards. Edwards simply does not disclose *drug particle* compositions wherein the geometric diameter of the component drug particles is less than 5 μm. The difference in drug particle size of less than about 1 μm for the claimed invention and at least 5 μm for Edwards has significant consequences, as it is the nanoparticulate particle size of the component drug particles which enables the superior properties of the claimed compositions. *See* the specification at pages 5 – 6. Although Edwards makes reference to particles of between 50 and 100 μm in diameter (column 4, lines 22-25), these comprise optionally co-delivered carrier particles not carrying a therapeutic agent.

For example, Applicants' claimed dry powder compositions comprising nanoparticulate drugs result in an increase in the number of drug particles per unit dose and a consequent distribution of the nanoparticulate drug particles over a larger physiological surface area as compared to the same quantity of delivered micronized drug, such as the drug compositions disclosed by Edwards. For systemic delivery *via* the pulmonary route, this approach takes maximum advantage of the extensive surface area presented in the alveolar region – thus producing more favorable drug delivery profiles, such as a more complete absorption and rapid onset of action.

Moreover, the aerosol compositions of the present invention enable rapid nasal delivery. Nasal delivery of such aerosol compositions will be absorbed more rapidly and completely than micronized aerosol compositions because the nanoparticulate drug particles will dissolve before being cleared by the mucociliary mechanism.

The larger drug particle sizes of Edwards dissolve more slowly and, therefore, are absorbed more slowly than Applicants' claimed compositions. In some cases the drug particles of Edwards may not be fully absorbed before being cleared by the mucociliary mechanism.

Because Edwards does not disclose each and every limitation of the claimed invention as is required for a proper rejection under section 102(e), this ground for rejection should be withdrawn.

IV. Rejections Under 35 U.S.C. § 103(a)

A. Edwards et al.

Claims 11 – 34, 40, 41, 44, 45, 47, 48, 51 – 62, 69 – 96, and 111 – 117 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Edwards. Applicants respectfully traverse this ground for rejection.

1. The Examiner's Basis for the Rejection

The Examiner asserted, *inter alia*, that Edwards teaches "aerosol particle compositions that are less than 100 microns in diameter and have a surface modifier adsorbed thereon." Office Action, page 5. The Examiner concluded that the compositions of the claimed invention and those of Edwards "do not appear to be different." Applicants respectfully disagree.

2. Edwards Does Not Teach Applicants' Claimed *Drug* Particle Size

As noted above, Edwards does not teach the sub-micron particle size of the component drug particles of the claimed invention. The drug particles of Edwards are at least

5 μm in diameter, whereas those of the claimed invention are less than about 1 μm in diameter.

This distinction is significant as the nanoparticulate particle size of the component drug particles results in dramatically superior benefits as compared to prior art aerosol compositions. *See* the discussion, above.

Furthermore, Edwards does not teach or suggest spray drying of insoluble drug particles. The experiments cited in Edwards' Example 2 all refer to spray drying solutions of drug substance. It is not obvious from Edwards that inhalable particles can be achieved by spray drying suspensions of drug particles, and it is only because of the small drug particle size of the present invention (*i.e.*, < 1000 nm) that suitable powders can be achieved.

Because Edwards does not teach or suggest dry powder aerosol compositions comprising nanoparticulate drug particles of about 1 μm or less in diameter, it would not have been obvious to a person of ordinary skill in the art, armed with the teaching of Edwards, to make and use the claimed invention. For at least the foregoing reasons, Applicants respectfully withdrawal of this ground for rejection.

B. Edwards in View of Liversidge et al.

Claims 11 – 34, 40 – 45, 47, 48, 51 – 62, 65 – 96, and 97 – 117 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Edwards in view of Liversidge et al., U.S. Patent No. 5,145,684 ("Liversidge"). Office Action at page 6. Applicants respectfully traverse this ground for rejection.

1. The Examiner's Basis for the Rejection

The Examiner indicated that Liversidge teaches drug particle compositions that are less than 100 μm in diameter, that have a surface modifier adsorbed thereon, and that are used for the administration of drugs such as corticosteroids. Additionally, the Examiner alleged that Liversidge teaches a method of producing particles by a milling procedure, after which the particles are separated from the resultant dispersion by using a "sedimentation field flow

fractionator", thereby yielding particles that appear to be "the same as those of the instant claims."

The Examiner concluded that, "absent a demonstration between using a sedimentation field flow fractionator and evaporation," it would have been obvious for a person of ordinary skill in the art to combine the teachings of Edwards and Liversidge to arrive at the present aerosol corticosteroid particle formulations.

2. Edwards Does Not Teach Applicants' Claimed *Drug* Particle Size

Edwards fails to meet the limitations of the claimed invention for the reason set forth in the response to the §§ 102(e) and 103(a) rejections, above. That is, Edwards does not teach or suggest aerosol compositions comprising nanoparticulate drug particles of about 1 μm or less.

3. Liversidge Does Not Remedy the Deficiencies of Edwards

Liversidge discloses nanoparticulate drugs for use in non-aerosol dosage forms. The claimed invention is a substantial improvement over the invention of Liversidge as it has now been discovered that nanoparticulate drugs can be effectively incorporated into aerosol dosage forms, including dry powder dosage forms.

This discovery was unexpected, even though aerosol dosage forms such as those taught by Edwards were known, because aerosol dosage forms can be extremely difficult to design. For example, Edwards teaches that difficulties for the aerosol delivery of macromolecules include:

> protein denaturation during aerosolization, excessive loss of inhaled drug in the oropharyngeal cavity (often exceeding 80%), poor control over the site of deposition, lack of reproducibility of therapeutic results owing to variations in breathing patterns, the frequent too-rapid absorption of drug potentially resulting in local toxic effects, and phagocytosis by lung macrophages.

See Edwards at col. 1, lines 33 – 42.

Moreover, prior to Applicants' claimed invention, it was not known whether liquid formulations of nanoparticulate could be processed into dry powder aerosols of nanoparticulate drugs having suitable aerodynamic properties.

This is significant in that a primary challenge that must be overcome in the preparation of many dry powder aerosols is the avoidance of particulate aggregation, which is caused by particle-particle interactions, such as hydrophobic, electrostatic, and capillary interactions. An effective dry-powder inhalation therapy for both short and long term release of therapeutics, either for local or systemic delivery, requires a powder that displays minimum aggregation, as well as a means of avoiding or suspending the lung's natural clearance mechanisms until drugs have been effectively delivered. *See* Edwards at col. 3, lines 22 – 30.

Such difficulties in designing aerosol dosage forms of dry powder drug compositions, which were well known in the art at the time the claimed invention was made, would have made one of ordinary skill in the art unable to make the claimed compositions with any reasonable expectation of success, given the teachings of Edwards and Liversidge.

4. The Examiner's Comments Regarding Sedimentation Field Flow Fractionation

The Examiner contended that a combination of Edwards and Liversidge renders the claimed invention obvious "absent a demonstration between using a sedimentation field flow fractionator and evaporation." Office Action at page 6.

Applicants courteously point out that a sedimentation field flow fractionator is employed to *measure particle size*. See Liversidge, col. 5, lines 20 – 24. Sedimentation field flow fractionation does not refer to a method of obtaining small particles.

C. Edwards in View of Dalby et al.

Claims 35, 36, 49, 63, and 64 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Edwards in view of Dalby et al., U.S. Pat. No. 5,202,110 ("Dalby"). Office Action at page 7. Applicants respectfully traverse this ground for rejection.

1. The Examiner's Basis for the Rejection

Dalby discloses formulations for the delivery of a certain drug in pMDI's that contain non-chlorofluorocarbon ("non-CFC") propellants. The Examiner asserted that it would have been obvious to one of ordinary skill in the art to combine the drug particle compositions of Edwards with the non-CFC propellants of Dalby to obtain Applicants' claimed aerosol compositions. Applicants respectfully disagree.

2. Dalby Does Not Remedy the Deficiencies of Edwards

As noted above, Edwards does not teach or suggest aerosol compositions comprising nanoparticulate drug particles of about 1 μm or less in diameter. Dalby fails to remedy this deficiency. Thus, Edwards in combination with Dalby does not teach or suggest the claimed invention. Accordingly, withdrawal of this ground for rejection is respectfully requested.

V. Conclusion

In view of the foregoing amendments and remarks, the claimed invention is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

Examiner Ware is invited to contact the undersigned by telephone if he believes that a telephone interview would advance the prosecution of the present application.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: Nov 27, 2001

By: _____

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Marked-Up Version of Amended Claims to Show Changes Made

14. (Amended) The aerosol composition of claim 11, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

25. (Amended) The aerosol composition of claim 23, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

43. (Four Times Amended). A method of making an aerosol composition comprising:

(a) milling under pressurized conditions in a non-aqueous medium the following:

(i) a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in the non-aqueous dispersion medium of less than about 10 mg/ml, and

(ii) a surface modifier, to obtain a drug having an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm;

(b) evaporating the non-aqueous medium to obtain a dry powder of aggregates of drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns; and

(c) formulating the dry powder aggregates into an aerosol composition.

71. (Amended) The aerosol composition of claim 19, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

73. (Amended) The aerosol composition of claim 20, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

75. (Amended) The aerosol composition of claim 22, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

77. (Amended) The aerosol composition of claim 30, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

79. (Amended) The aerosol composition of claim 31, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

81. (Amended) The aerosol composition of claim 33, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

83. (Amended) The aerosol composition of claim 35, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies,

therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

97. (Amended) The aerosol composition of claim 42, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

104. (Amended) The aerosol composition of claim 43, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

111. (Amended) The aerosol composition of claim 44, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.